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Stereospecific approach to α,β-disubstituted nitroalkenes via coupling of α-bromonitroalkenes with boronic acids and terminal acetylenes

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Abstract—(*Z*)-α-Bromo-β-substituted nitroethylenes undergo facile Suzuki coupling with aryl, heteroaryl, and vinylboronic acids in the presence of $Pd(PPh_3)_4$ as catalyst to afford (*E*)-α,β-disubstituted nitroethylenes in high yield (up to 95%) and complete specificity. Similar coupling of α-bromonitroethylenes with terminal acetylenes (Sonogashira coupling) provides a novel route to (*E*)-nitroenynes. These Pd-catalyzed coupling methods offer a convenient and stereospecific entry into a diverse array of synthetically and biologically useful α,β-disubstituted nitroethylenes.

1. Introduction

Conjugated nitroalkenes are important building blocks in organic synthesis by virtue of their versatile reactivity as Michael acceptors, dipolarophiles, 1,3-dipoles, dienophiles, and heterodienes.[1] Nitroalkenes are also distinguished by their diverse biological activities.[2] Among various methods available for the preparation of nitroalkenes, Henry reaction (condensation of carbonyl compounds with nitroalkanes) followed by β-elimination of the resulting 2-nitroalcohols by direct dehydration or after activation of the hydroxyl group is primarily the method of choice.[3] However, this method is ineffective for the preparation of isomerically pure α,β-disubstituted nitroalkenes because of the possible formation of (*E*) and (*Z*)-nitroalkenes from diastereomeric nitroaldols. Similar condensation of nitroalkanes with Schiff's bases generally provides low yields of nitroalkenes due to instability of Schiff's bases and are substrate specific.[4] Other methods for the preparation of nitroalkenes include direct nitration of alkenes with nitryl halides,[5] Cu(II)–$NaNO_2$ complex,[6] dinitrogen tetroxide,[7] ceric ammonium nitrate (CAN),[8] nitrodecarboxylation,[9] and treatment of nitronates with phenylselenylbromide followed by elimination.[10] However, many of these methods are prone to side reactions and are specific to a narrow range of substrates. Recently, condensation of aldehydes with 1-nitroalkanephosphonates (modified Horner–Wadsworth–Emmons reaction)[11] and nitroacetonitrile (Knoevenagel reaction)[12] was reported for the synthesis of α,β-disubstituted (*E*)-nitroalkenes. However, these condensations worked satisfactorily only with aromatic aldehydes. Our own group has reported α-hydroxyalkylation, aminoalkylation, and hydrazination of a variety of β-aryl nitroethylenes via Morita–Baylis–Hillman reaction.[13] In most cases, the products isolated were isomerically pure α,β-disubstituted (*E*)-nitroalkenes. However, α-alkylation could be carried out only with selected electrophiles such as methyl vinyl ketone and acrylate. Therefore, simple alkylation, arylation, alkynylation, etc. of the α-position of nitroalkenes remain largely unexplored.

In view of the above, a general and practical route to a variety of α,β-disubstituted nitroalkenes appeared desirable. Owing to the efficacy and functional group tolerance of transition metal catalyzed cross-coupling reactions, particularly with the advent of novel catalyst systems, in forming C–C and C–X (X=O, N, S) bonds,[14] we envisioned that such coupling of α-bromonitroethylenes with suitable nucleophilic partners, namely, alkyl and arylboronic acids (Suzuki–Miyaura reaction)[15,16] and terminal acetylenes (Sonogashira–Hagihara reaction)[17–19] would provide an array of synthetically and biologically relevant α,β-disubstituted (*E*)-nitroalkenes. Although cross-coupling reactions of boronic acid derivatives with various electron-deficient haloalkenes were reported in the literature,[20,21] such reactions of α-halonitroalkenes has not received much attention.[22] Previous attempts to carry out Pd-catalyzed reactions of α-bromonitroalkenes provided mixture of products (Scheme 1a),[23] or led to the conjugate addition of the ligand (triphenylphosphine) and further transformation (Scheme 1b).[24] In some

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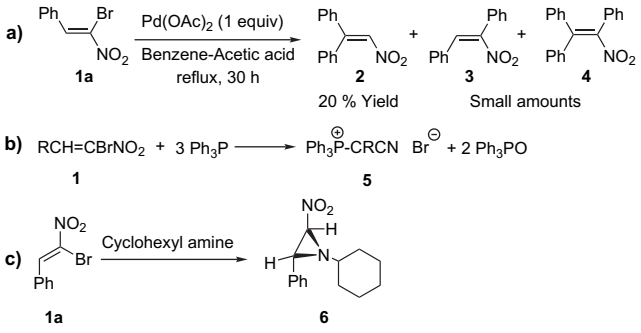
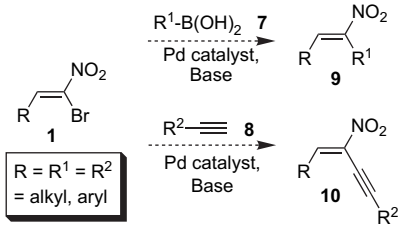
cases, the nitro group was replaced by nucleophiles via one-electron transfer processes ($S_{RN}1$).[25] Similarly, although Sonogashira coupling of many activated and unactivated haloalkenes with terminal acetylenes under the co-catalytic influence of amines was reported in the literature,[26] to our knowledge, α-bromonitroalkenes were not employed in such capacity. In fact, reaction of bromonitroalkene **1a** with primary amines provided aziridine **6** as the sole product (Scheme 1c).[27]



Scheme 1.

It is obvious from the above discussion that controlling chemo-, stereo-, and regioselectivities in cross-coupling reactions involving highly reactive substrates, such as **1**, would be of considerable interest. This together with our ongoing efforts toward developing new strategies involving nitroalkenes,[13,28] we sought to investigate the cross-coupling reactions, viz. Suzuki and Sonogashira reactions, of α-bromo-nitroalkene **1**, for the stereospecific synthesis of α,β-disubstituted (*E*)-nitroalkenes **9** and **10** (Scheme 2).



Scheme 2.

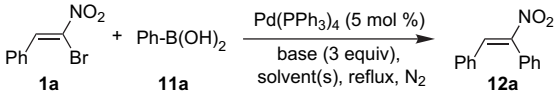
2. Results and discussion

We initially set out to carry out Suzuki–Miyaura coupling of (*Z*)-α-bromonitroalkenes **1**. Since the C–B bond is weakly polarized, organo-boron compounds are weakly nucleophilic. Therefore, they are expected to undergo fast transmetallation rather than taking part in conjugate addition. However, in view of the unusual reactivity of conjugated nitroalkenes with metal-based reagents,[29] we felt that appropriate choice of palladium catalyst, base, and solvent would be necessary for obtaining the cross-coupled products in significant yields.

The α-bromonitroalkenes **1** required for the present study were readily prepared by a one pot bromination/dehydrobromination protocol.[30] The stereochemistry was assigned to be (*Z*) based on the literature.[31] An initial experiment performed by refluxing (*Z*)-1-bromo-1-nitrophenylethene **1a** and phenylboronic acid **11a** in toluene in the presence of potassium carbonate (3 equiv) and $Pd(PPh_3)_4$ (5 mol %) as catalyst provided the coupled product **12a** in 50% yield (Table 1, entry 1).[32] Either poor yield or a complex mixture was encountered when the reaction was carried out in other hydrocarbon solvents (Table 1, entries 2 and 3), and polar protic and aprotic solvents (entries 4–7). Finally, a mixture of solvents such as toluene, ethanol, and water (in 9:0.5:0.5) provided higher yield of **12a** (64%, Table 1, entry 11). At this stage, we screened other bases, which were previously employed in Suzuki–Miyaura coupling reactions. While changing the base from K_2CO_3 to Na_2CO_3 or KOH did not have any appreciable influence on the yield (Table 1, entries 12 and 13), $Ba(OH)_2\cdot 8H_2O$ and NaH_2PO_4 were not found suitable (entries 14 and 15). On the other hand, bicarbonates provided improved yields of **12a** in shorter reaction times (1.5 h, Table 1, entries 16 and 17).

At this stage, it appeared necessary to optimize the amounts of boronic acid **11a** and $Pd(PPh_3)_4$, and also screen other Pd catalysts in the reaction (Table 2). Entries 1–6 (Table 2) show that the most economical combination is 1.5 equiv of boronic acid **11a** and 2.5 mol % of $Pd(PPh_3)_4$ (entry 4). Other Pd(0) and Pd(II) catalysts screened under the above conditions in the presence and absence of additives were less effective (Table 2, entries 7–16). Having optimized the cross-coupling of bromonitroalkene **1a** with phenylboronic acid **11a**, we turned our attention to the scope of the reaction by screening various α-bromonitroalkenes **1b–h** and phenylboronic acid **11a** (Table 3). The procedure was found equally suitable for β-aryl (entries 1–4), β-heteroaryl (entries 5 and 6), and β-alkyl (entries 7 and 8) nitroethylenes **1a–h** providing high yields of the coupled products **12a–h** (76–86%, Table 3).

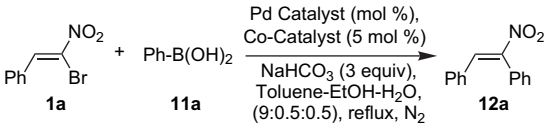
Table 1. Screening of various solvents and bases in Suzuki–Miyaura cross-coupling reaction of α-bromonitroalkene **1a**[a]



Entry	Solvent(s)	Base	Time (h)	Yield[b] (%)
1	Toluene	K_2CO_3	8	50
2	*n*-Heptane	K_2CO_3	12	40
3	Cyclohexane	K_2CO_3	12	24
4	Ethanol	K_2CO_3	2	12
5	THF	K_2CO_3	8	42
6	Acetonitrile	K_2CO_3	5	—[c]
7	DMF	K_2CO_3	5	—[c]
8	Dioxane–water (8.3:1.7)	K_2CO_3	3	50
9	Toluene–ethanol–water (5:2.5:2.5)	K_2CO_3	12	32
10	Toluene–ethanol–water (7.4:1.3:1.3)	K_2CO_3	12	40
11	Toluene–ethanol–water (9:0.5:0.5)	K_2CO_3	4	64
12	Toluene–ethanol–water (9:0.5:0.5)	Na_2CO_3	4.5	58
13	Toluene–ethanol–water (9:0.5:0.5)	KOH	2	60
14	Toluene–ethanol–water (9:0.5:0.5)	$Ba(OH)_2\cdot 8H_2O$	2	45
15	Toluene–ethanol–water (9:0.5:0.5)	NaH_2PO_4	3	28
16	Toluene–ethanol–water (9:0.5:0.5)	$KHCO_3$	1.5	62
17	**Toluene–ethanol–water (9:0.5:0.5)**	**$NaHCO_3$**	**1.5**	**68**

[a] All reactions were conducted on a 0.2 mmol scale of **1a**, using 1.3 equiv of phenylboronic acid **11a**.
[b] Isolated yield after purification by silica gel column chromatography.
[c] Complex mixture.

Table 2. Screening of Pd catalyst and optimization of the amount of Pd catalyst and boronic acid **11a**



1a **11a** **12a**

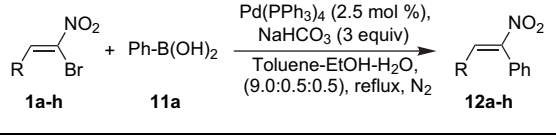
Entry	**11a** (equiv)	Pd catalyst	mol %	Co-catalyst	Time (h)	Yield[a] (%)
1	1.3	$Pd(PPh_3)_4$	5.0	—	1.5	68
2	1.5	$Pd(PPh_3)_4$	5.0	—	1.5	75
3	2.0	$Pd(PPh_3)_4$	5.0	—	1.5	76
4	**1.5**	**$Pd(PPh_3)_4$**	**2.5**	—	**6.5**	**76**
5	1.5	$Pd(PPh_3)_4$	1.0	—	8.0	65
6	1.5	$Pd(PPh_3)_4$	0.5	—	40.0	20[b]
7	1.5	Pd–C	2.5	—	48.0	<5[c]
8	1.5	$PdCl_2$	2.5	PPh_3	12.0	52
9	1.5	$Pd(OAc)_2$	2.5	PPh_3	2.5	62
10	1.5	$Pd(OAc)_2$	2.5	PPh_3	2.5	—[d]
11	1.5	$Pd(OAc)_2$	2.5	Et_3N	5.0	Traces
12	1.5	$PdCl_2$	2.5	—	12.0	12[c]
13	1.5	$Pd(OAc)_2$	2.5	—	8.0	—[e]
14	1.5	$Pd(dba)_2$	2.5	—	4.5	56
15	1.5	$PdCl_2(PPh_3)_2$	2.5	PPh_3	5.0	70
16	1.5	$PdCl_2$(dppe)	2.5	PPh_3	4.0	56

[a] Isolated yield after purification by silica gel column chromatography.
[b] Bromonitroalkene **1a** (~50%) was recovered.
[c] By ^1H NMR.
[d] No reaction in the absence of $NaHCO_3$.
[e] Polymerization.

Subsequently, boronic acids other than **11a** were screened for the coupling reaction with **1a** (Table 4). For instance, reaction of arylboronic acids **11b–e** with bromonitroalkene **1a** provided the coupled products **12i–l** in excellent yields (82–95%, Table 4, entries 1–4). While the cross-coupling of **1a** with 2-furyl, 2-thienyl, and 2-phenethylboronic acids, **11f**, **11g**, and **11j**, respectively, failed to give the desired products **12m**, **12n**, and **12q** (Table 4, entries 5, 6, and 9), similar coupling of **1a** with 3-thienyl and α-phenyl vinylboronic acids, **11h** and **11i**, respectively, provided the products **12o** and **12p** in high yields (Table 4, entries 7 and 8).

An electron-deficient diene with one terminal unsubstituted **12p** has been synthesized in high yield (85%) from **1a** and

Table 3. Cross-coupling of various α-bromonitroalkenes **1a–h** with phenylboronic acid **11a**[a,b]

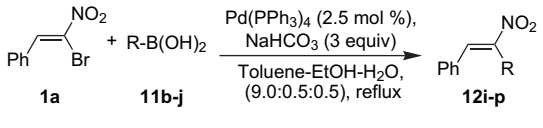


1a-h **11a** **12a-h**

Entry	**1**	R	Time (h)	Yield[c] of **12a–h** (%)
1	**1a**	Ph	6.5	76
2	**1b**	4-OMe–Ph	6	79
3	**1c**	3,4-(OCH_2O)–Ph	10	80
4	**1d**	4-F–Ph	28	76
5	**1e**	2-Furyl	1.5	76
6	**1f**	2-Thienyl	5	86
7	**1g**	n-C_6H_{13}	1	81
8	**1h**	Me_2CHCH_2	1.5	78

[a] The reaction scale w.r.t. bromonitroalkene **1** was 0.5 mmol for entries 1–7 and 0.25 mmol for entry 8.
[b] Concentration of the reaction mixture was 0.04 M for entries 1–3 and 5–8 and 0.08 M for entry 4.
[c] Isolated yield after purification by silica gel column chromatography.

Table 4. Cross-coupling of α-bromonitrostyrene **1a** with boronic acids **11b–j**

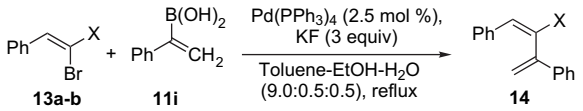


1a **11b-j** **12i-p**

Entry	**11**	R	**12**	Time (h)	Yield[a] (%)
1	**11b**	4-Me–Ph	**12i**	6.0	91
2	**11c**	4-C_2H_5–Ph	**12j**	7.0	90
3	**11d**	4-MeO–Ph	**12k**	3.5	95
4	**11e**	2-Naphthyl	**12l**	3.5	82
5	**11f**	2-Furyl	**12m**	1.0	—[b]
6	**11g**	2-Thienyl	**12n**	1.0	—[b]
7	**11h**	3-Thienyl	**12o**	30.0	75
8	**11i**	α-Phenylvinyl	**12p**	4.0	85
9	**11j**	2-Phenethyl	**12q**	42.0	—[c]

[a] Isolated yield after purification by silica gel column chromatography.
[b] Complex mixture.
[c] No reaction even after using 10 mol % of $Pd(PPh_3)_4$.

11i by our methodology (Table 4, entry 8). We extended the scope of Suzuki coupling of **11i** with other 1-bromoolefins **13** for the selective formation of terminally unsubstituted dienes, which are otherwise difficult to synthesize (Scheme 3). This coupling provides a variety of uniquely functionalized electron-deficient dienes **14a** and **14b**, which are presumably good substrates for Diels–Alder cycloaddition. The formation of the (*E*) isomer with high stereospecificity and high yields rules out the possible complexation of Pd(0) species with the olefinic bond or the NO_2 group and confirms that the classical Suzuki coupling mechanism is operational in the coupling of α-bromonitroalkene **1** with boronic acids **11**. The inability of 2-furyl- and 2-thienylboronic acids, **11f** and **11g**, respectively, to take part in cross-coupling is attributable to their relatively electron-deficient nature.



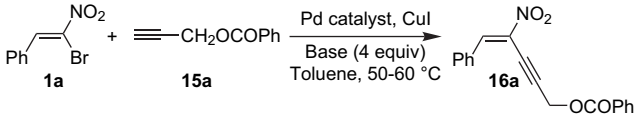
13a-b **11i** **14**

14a: X = CHO, 18 h, 82% yield
14b: X = CO_2Et, 15 h, 88% yield

Scheme 3.

Our next objective was to investigate the coupling of α-bromonitroalkenes **1** with terminal alkynes under Pd-catalyzed conditions (Sonogashira reaction). α-Bromonitrostyrene **1a** and propargyl benzoate **15a** were chosen as model substrates for the coupling reaction in the presence of 2.5 mol % of $Pd(PPh_3)_4$ in toluene at reflux temperature (Table 5). Several bases were systematically screened for their co-catalytic activity. Either no reaction or low yield of the desired product **16a** was encountered when tertiary amine bases such as triethylamine, DBU, pyridine, and Hünig's base were employed (Table 5, entries 1–4). When *N*-methylmorpholine was used as the base, the cross-coupled product **16a**, though isolated in 56% yield, was contaminated by the homo-coupled product of alkyne **15a** (Table 5, entry 5). This prompted us to optimize the amount of cuprous iodide and other non-amine bases, which have been extensively used in Sonogashira reaction.[17–20] Reducing the amount of CuI from 10 mol % to

Table 5. Optimization of conditions for Sonogashira–Hagihara cross-coupling



Entry	Pd catalyst (2.5 mol %)	Base (4 equiv)	CuI (mol %)	Time (h)	Yield[a] (%)
1	$Pd(PPh_3)_4$	Triethylamine	10	8	10
2	$Pd(PPh_3)_4$	DBU	10	8	—[b]
3	$Pd(PPh_3)_4$	*i*-Pr_2NEt	10	4	29
4	$Pd(PPh_3)_4$	Pyridine	10	12	—[b]
5	$Pd(PPh_3)_4$	NMM	10	5	56[c]
6	$Pd(PPh_3)_4$	NMM	5.0	3	70
7	$Pd(PPh_3)_4$	NMM	2.5	3	72
8	$Pd(PPh_3)_4$	NMM	—	24	—[b]
9	$Pd(PPh_3)_4$	Cs_2CO_3	2.5	6	—[b]
10	$Pd(PPh_3)_4$	KO^{t}Bu	2.5	6	—[b]
11	$Pd(PPh_3)_4$	TBAB	2.5	6	—[b]
12	$Pd(PPh_3)_4$	TBAF (in THF)	2.5	6	—[b]
13	$Pd(dba)_2$	NMM	2.5	22	50[d]
14	$PdCl_2(PPh_3)_2$[e]	NMM	2.5	5	77
15	$PdCl_2$(dppe)[e]	NMM	2.5	8	42
16	$Pd(PPh_3)_4$	NMM[f]	2.5	2	72

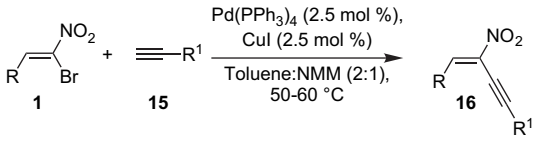
[a] Isolated yield after purification by silica gel column chromatography.
[b] No reaction.
[c] ^1H NMR suggested significant amount (25–35%) of dimerized product of alkyne **15a**, even after repeated purification.
[d] % Conversion.
[e] PPh_3 of 5 mol % as an additive.
[f] Toluene–NMM (2:1).

5 mol % had a beneficial effect (Table 5, entry 6) and further reduction in the amount of CuI to 2.5 mol % maintained a good yield (72%, entry 7). However, there was no reaction in the absence of CuI even after 24 h (Table 5, entry 8). Similarly, no reaction was observed when non-amine bases were employed (Table 5, entries 9–12). Finally, other catalysts such as $Pd(dba)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2$(dppe), which are known to promote Sonogashira coupling provided unsatisfactory results (Table 5, entries 13–15). The poor performance of Pd(II) pre-catalysts is attributable to the propensity of α-bromonitroalkene to react with triphenylphosphine as discussed above (see Scheme 1b).[24] Finally, when we employed NMM as co-solvent (toluene–NMM ratio 2:1), a fast reaction occurred providing good yield (72%) of cross-coupled adduct (Table 5, entry 16).

Having optimized the conditions for the cross-coupling of α-bromonitroalkene **1a** with terminal acetylene **15a**, a variety of aromatic, heteroaromatic, and aliphatic α-bromonitroalkenes **1a**, **1b**, **1e**, **1f**, **1h**, and **1i** were reacted with several terminal alkynes **15a–f** in the presence of 2.5 mol % each of $Pd(PPh_3)_4$ and CuI in toluene–NMM at 50–60 °C (Table 6). The coupling of bromonitroalkene **1a** with phenylacetylene **15b** provided the product **16b** in 69% yield after prolonged heating (22 h, Table 6, entry 2). Substantial rate acceleration with improvement in the yield (8 h, 76%) was observed when 4-fluoro-phenylacetylene **15c** was reacted with **1a** (Table 6, entry 3). In the presence of excess CuI (10 mol % instead of 2.5 mol %), such couplings required longer reaction times and provided the desired products in lower yields due to homo-coupling. While terminal acetylenes **15e** and **15f** also reacted smoothly with **1a** (Table 6, entries 5 and 6), 2-furylacetylene **15d** failed to react with **1a** even after employing a variety of conditions (entry 4). Subsequently, substituted aromatic nitroalkenes **1b** and **1i** and heteroaromatic ones **1e** and **1f** were reacted with acetylene **15a** to afford the coupled products in high yield (70–84%, Table 6, entries 7, 12, 8, and 9, respectively). The heteroaromatic bromonitroalkene **1f** also reacted well with *n*-octyne **15f** to provide the coupled product **16j** in 86% yield (Table 6, entry 10). However, attempted coupling of an aliphatic bromonitroalkene **1h** with **15a** yielded only a complex mixture (Table 6, entry 11).

Sonogashira coupling generally involves amines (tertiary, secondary or primary) as primary organic bases, which are

Table 6. Palladium-catalyzed Sonogashira–Hagihara cross-coupling of α-bromonitroalkenes **1** with terminal alkynes **15**



Entry	**1**	R	**15**	R^1	**16**	Time (h)	Yield[a] (%)
1	**1a**	Ph	**15a**	CH_2OCOPh	**16a**	2	72
2	**1a**	Ph	**15b**	Ph	**16b**	22	69[b]
3	**1a**	Ph	**15c**	4-F–Ph	**16c**	8	76[b,d]
4	**1a**	Ph	**15d**	2-Furyl	**16d**	22	—[c]
5	**1a**	Ph	**15e**	CH_2OBn	**16e**	6	70
6	**1a**	Ph	**15f**	*n*-C_6H_{13}	**16f**	8	85
7	**1b**	4-OMe–Ph	**15a**	CH_2OCOPh	**16g**	8	71
8	**1e**	2-Furyl	**15a**	CH_2OCOPh	**16h**	2	70
9	**1f**	2-Thienyl	**15a**	CH_2OCOPh	**16i**	4	80
10	**1f**	2-Thienyl	**15f**	*n*-C_6H_{13}	**16j**	2	86
11	**1h**	Me_2CHCH_2	**15a**	CH_2OCOPh	**16k**	24	—[e]
12	**1i**	4-Cl–Ph	**15a**	CH_2OCOPh	**16l**	1.5	84

[a] Isolated yield after purification by silica gel column chromatography.
[b] Toluene–NMM (1.0:1.5, 0.08 M).
[c] No reaction even after changing the solvent to dioxane, THF or CH_3CN.
[d] With excess CuI (10 mol %, see Table 5), the yields were low (61% and 62%, respectively, for entries 2 and 3) in these cases as well.
[e] Toluene–NMM (4:1, 2:1 or 2:3), complex mixture.

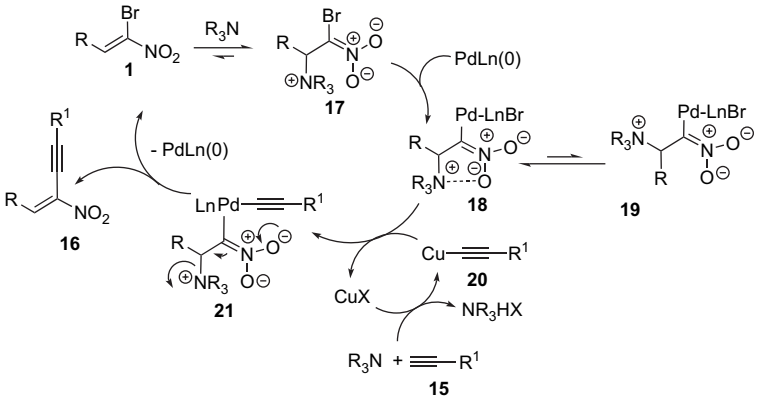
known to promote coupling by facilitating the formation of Cu-acetylide and by reducing the Pd(II) species to the much needed Pd(0) species.[17] However, both primary and secondary amines are unsuitable for the cross-coupling of bromonitroalkenes **1**, as they would react with nitroalkenes in a Michael fashion to form stable aziridines **6** (Scheme 1c) or β-aminonitroalkanes.[33] Although tertiary amines are also known to react with nitroalkenes in a 1,4-fashion, such reactions are reversible.[34] Therefore, the following mechanistic proposal rationalizes the formation of coupled products even if reversible Michael addition of tertiary amine to nitroalkene **1** does takes place (Scheme 4). Thus, NMM could undergo Michael type addition to provide nitronate, bearing α-halo substituent **17**. Oxidative addition of Pd(0) species to **17** will furnish the intermediate **18**. Although **18** could, in principle, be in equilibrium with **19**, the former is expected to be more stable due to electrostatic attraction between the ammonium and the nitronate moieties and the lack of such interaction in the latter. The intermediate **18** then undergoes usual transmetallation with alkynylcopper species **20** to afford the transmetallated adduct **21**. Elimination of NMM followed by reductive elimination of the palladium catalyst would provide the coupled product **16**.

2.1. Structure and stereochemistry

The geometry of the double bond in **12a** was confirmed to be (*E*) by comparison of its observed mp and ^{1}H NMR data with those in the literature (Fig. 1).[35,36] Mp and ^{1}H NMR data of **12b**,[35] **12c**,[35] **12e**,[37] and **12f**[37] were also consistent with the literature data. The stereochemistry was further independently confirmed by analysis of the ^{1}H–^{1}H NOESY spectrum of a representative coupled product. Thus, a weak to medium NOE between the aryl protons and the protons of the alkyl chain was observed in **16f** indicating the (*E*)-configuration of the double bond. By analogy, the double bond geometry of other cross-coupled adducts **12b–p**, **14a–b**, and **16a–l** was assigned. The chemical shifts of β-hydrogens in cross-coupled adducts suggest a formidable deshielding effect (see Fig. 1 and experimental in Supplementary data), which is not consistent with (*Z*)-structure where the interaction between the phenyl ring and the olefinic proton should be the same as in analogous systems, e.g. (*Z*)-α-phenyl-β-arylacrylic acids[38] and the (*Z*)-α-phenylcinnamic acids.[39] Consequently, the (*E*)-configuration can be unambiguously assigned to all the cross-coupled adducts, in which a marked anisotropic deshielding of the olefinic H occurs owing to the adjacent nitro group, again, analogous to that in (*E*)-α-phenyl-β-arylacrylic acids.[38]

Subsequent to the above stereochemical analysis, the configuration of dienes **12p**, **14a**, and **14b** was examined. Although NOE experiment was not very informative in the case of **12p** (weak NOE between one of the terminal vinylic protons and the aromatic protons) due to overlapping of the aromatic protons, cisoid structure was assigned for **12p** based on the unambiguous assignment of analogous systems, viz. **14a** and **14b** (Fig. 1). Thus, the presence of a medium NOE between the aldehyde proton and the aromatic protons, and the absence of any NOE between the aldehyde protons and the olefinic methylene protons confirmed the cisoid structure **14a**. Similarly, the presence of weak NOE between the methyl group and the aromatic protons, and the absence of any NOE between the methyl group and the terminal olefinic methylene protons unambiguously established the cisoid structure for **14b**.

The synthetic utility of the coupled products was demonstrated by the following representative reactions using



Scheme 4.

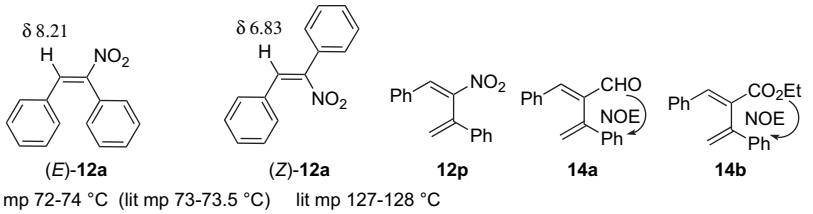
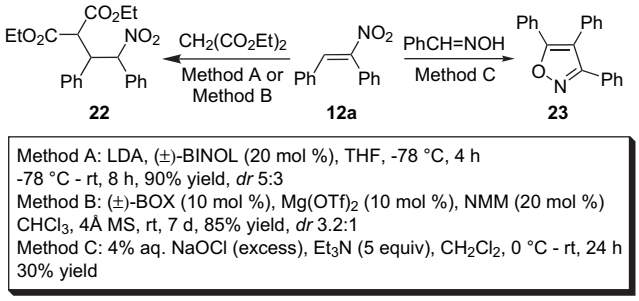


Figure 1.

nitroalkene **12a**. Thus, Michael addition of diethyl malonate to **12a**, mediated by LDA/BINOL, provided the adduct **22** in 90% yield and 5:3 dr (Scheme 5). However, better diastereoselectivity (3.2:1)[40] was obtained when the addition was performed under Lewis acid catalyzed (BOX, $Mg(OTf)_2$) conditions.[41] Similarly, 1,3-dipolar cycloaddition of **12a** with benzonitrile oxide, generated in situ from benzaldoxime,[42] furnished 3,4,5-triphenylisoxazole **23** in moderate (30%) yield via intermediate cycloadduct, which presumably underwent elimination of HNO_2.



Scheme 5.

3. Conclusions

α-Bromonitroethylenes possessing aryl, heteroaryl, and alkyl groups at the β-position could be utilized to synthesize α,β-disubstituted nitroethylenes in which the new α-substituent could be aryl, heteroaryl, alkynyl, etc., via Pd-catalyzed Suzuki and Sonogashira type coupling reactions. The reaction proceeded well in the presence of $Pd(PPh_3)_4$ as the catalyst and provided the coupled products in good to excellent yields. Various boronic acids and terminal acetylenes were used as coupling partners in these reactions. The remarkable feature of these reactions is the stereospecific formation of (*E*) isomers from (*Z*)-α-bromonitroethylenes.

4. Experimental

4.1. General

Unless otherwise noted all reagents were purchased from commercial sources and used without further treatment. THF was freshly distilled from sodium-benzophenone ketyl under nitrogen atmosphere. Other solvents were dried by standard methods. The reactions were conducted using flame-dried flasks under steady stream of dry nitrogen. All solvents were either sonicated or degassed under vacuum before use. Melting points were uncorrected. IR spectra (KBr/film) were recorded on a NICOLET IR 200 or Perkin–Elmer Spectrum One FT-IR spectrometer. ^1H NMR, ^{13}C NMR, ^{19}F NMR, 2D-HSQC, and 2D-NOESY were recorded on a Varian Mercury Plus OXFORD AS 400 NMR spectrometer (broad band and auto-switchable probes). The chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) for ^1H and ^{13}C and CF_2Cl_2 for ^{19}F. Mass spectrometric (MS) data were obtained by electrospray ionization (ESI) on a Micromass Q-TOF micro™ Mass Spectrometer.

Pd catalysts $Pd(dba)_2$,[43] $PdCl_2(PPh_3)_2$,[44] and $Pd(dppe)Cl_2$[45] were freshly prepared following the literature methods. Phenylboronic acid **11a**, 4-ethylphenylboronic acid **11c**, 4-methoxyphenylboronic acid **11d**, and 2-furylboronic acid **11f** were prepared from the corresponding halides by halogen–lithium exchange followed by treatment with tri-*n*-methylborate or tri-*n*-butylborate and acidic hydrolysis.[46] Other boronic acids were commercially available. Terminal acetylenes **15a**–**f**[47] and bromonitroalkenes **1a**–**i**[30a] were prepared following the literature methods (see Supplementary data for further details).

4.2. General procedure for Suzuki–Miyaura cross-coupling of α-bromonitroalkenes 1, bromoaldehyde 13a, and bromoester 13b with boronic acids 11 (Tables 3 and 4 and Scheme 3)

To a stirred suspension of boronic acid **11** (8 mmol, 1.5 equiv w.r.t. **1** or **13**), sodium bicarbonate (3 equiv for **1** and 3 equiv KF for **13a** and **13b**), toluene (9 ml), ethanol (0.5 ml), and water (0.5 ml) was added α-bromonitroalkene **1** or bromoaldehyde **13a** or bromoester **13b** (5.3 mmol), and the resulting mixture was stirred under nitrogen for 15 min. Then $Pd(PPh_3)_4$ (2.5 mol %) was added in one portion and the reaction mixture was slowly heated to reflux under a steady stream of nitrogen. After the completion of the reaction (monitored by TLC, see also Tables 3 and 4 and Scheme 3), the reaction mixture was cooled to ambient temperature and diluted with ether (20 ml) and filtered. After usual workup, the organic layer was concentrated in vacuo and the crude product was purified by silica gel column chromatography (EtOAc–hexanes, gradient elution) to provide pure coupled products **12** or **14**. The products were further purified by recrystallization from ethanol or ether–hexane mixture. Experimental data for compounds **12a**–**f** are consistent with the literature (see Supplementary data).

4.2.1. 1-[(*E*)-1-Nitrooct-1-enyl)]benzene (12g). Light yellow liquid; yield 0.189 g (81%); IR (film, cm^{-1}) 3055 (m), 2930 (s), 2858 (m), 1652 (w), 1557 (m), 1524 (s), 1462 (m), 1334 (s), 1265 (s), 743 (vs), 704 (s); ^1H NMR ($CDCl_3$) δ 0.79 (t, J=7.1 Hz, 3H), 1.11–1.26 (m, 6H), 1.41 (quintet, J=7.7 Hz, 2H), 2.04 (q, J=7.7 Hz, 2H), 7.18–7.22 (m, 3H), 7.33 (t, J=8.0 Hz, 1H), 7.36–7.39 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 28.3, 28.4, 28.7, 31.3, 128.4, 129.4, 129.6, 130.3, 138.7, 151.1; MS (TOF ES$^-$) *m/e* (rel intensity) 232 ([M−H]$^+$, 20); HRMS calcd for $C_{14}H_{18}NO_2$ ([M−H]$^+$) 232.1338, found 232.1346.

4.2.2. 1-[(*E*)-4-Methyl-1-nitropent-1-enyl)]benzene (12h). Light yellow liquid; yield 0.160 g (76%); IR (film, cm^{-1}) 3063 (w), 2958 (m), 2929 (m), 2858 (m), 1653 (m), 1525 (s), 1462 (w), 1334 (m), 1266 (w), 1244 (w), 1048 (w), 740 (s), 703 (m); ^1H NMR ($CDCl_3$) δ 0.91 (d, J=6.6 Hz, 6H), 1.83 (m, 1H), 2.02 (dd, J=8.0, 6.6 Hz, 2H), 7.24–7.27 (m, 2H), 7.40–7.47 (m, 3H), 7.42 (t, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.4, 28.3, 37.3, 128.5, 129.5, 129.7, 130.4, 137.8, 151.7; MS (MALDI TOF$^+$) *m/e* (rel intensity) 206 (MH$^+$, 23); HRMS calcd for $C_{12}H_{16}NO_2$ (MH$^+$) 206.1181, found 206.1180.

4.2.3. 1-Methyl-4-[(*E*)-1-nitro-2-phenylvinyl)]benzene (12i). Yellow solid; yield 0.217 g (91%); mp 65–66 °C

(*n*-hexane); IR (KBr, cm^{-1}) 3057 (w), 2919 (w), 1651 (s), 1515 (s), 1446 (m), 1321 (s), 1212 (w), 1119 (w), 971 (w), 764 (m), 689 (m); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 7.13 (d, J=7.6 Hz, 2H), 7.20–7.26 (m, 5H), 7.28 (d, J=7.6 Hz, 2H), 8.2 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 127.5, 128.6, 129.9, 130.3, 130.6, 131.1, 131.3, 134.5, 140.2, 149.7; MS (TOF ES$^+$) *m/e* (rel intensity) 262 (MNa^+, 45), 193 (100); HRMS calcd for $C_{15}H_{13}NO_2Na$ (MNa^+) 262.0844, found 262.0856.

4.2.4. 1-[(*E*)-2-(4-Ethylphenyl)-2-nitrovinyl)]benzene (12j). Yellow solid; yield 0.227 g (90%); mp 88 °C (*n*-hexane); IR (KBr, cm^{-1}) 3028 (w), 3008 (w), 2978 (w), 2935 (w), 2835 (w), 1649 (m), 1605 (m), 1515 (s), 1453 (m), 1369 (m), 1321 (s), 1292 (m), 1246 (s), 1169 (m), 1027 (m), 770 (m), 690 (m); ^1H NMR ($CDCl_3$) δ 1.21 (t, J=7.6 Hz, 3H), 2.65 (q, J=7.6 Hz, 2H), 7.03 (d, J=7.7 Hz, 2H), 7.11–7.18 (m, 5H), 7.22 (d, J=7.7 Hz, 2H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 28.7, 127.6, 128.6, 128.7, 130.4, 130.6, 131.0, 131.3, 134.5, 146.3, 149.8; MS (TOF ES$^+$) *m/e* (rel intensity) 276 (MNa^+, 45), 207 (100); HRMS calcd for $C_{16}H_{15}NO_2Na$ (MNa^+) 276.1000, found 276.1001.

4.2.5. 1-[(*E*)-2-(4-Methoxyphenyl)-2-nitrovinyl]benzene (12k). Yellow solid; yield 0.242 g (95%); mp 95–96 °C (*n*-hexane–EtOAc 9.5:0.5); IR (KBr, cm^{-1}) 3008 (w), 2974 (w), 2934 (w), 2835 (w), 1650 (w), 1606 (m), 1515 (s), 1453 (m), 1369 (m), 1321 (s), 1246 (s), 1168 (m), 1028 (m), 770 (m), 690 (m); ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 6.90 (d, J=8.3 Hz, 2H), 7.04 (d, J=8.3 Hz, 2H), 7.13–7.27 (m, 5H), 8.1 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.3, 114.7, 122.5, 128.7, 130.6, 131.0, 131.5, 132.0, 134.3, 149.6, 160.8; MS (TOF ES$^+$) *m/e* (rel intensity) 278 (MNa^+, 3), 209 (100); HRMS calcd for $C_{15}H_{13}NO_3Na$ (MNa^+) 278.0793, found 278.0796.

4.2.6. 2-[(*E*)-1-Nitro-1-phenylvinyl]naphthalene (12l). Yellow solid; yield 0.225 g (82%); mp 120 °C (*n*-hexane–ether 9:1); IR (KBr, cm^{-1}) 3062 (w), 2954 (w), 2924 (w), 1651 (m), 1515 (s), 1493 (m), 1320 (s), 1283 (m), 933 (m), 763 (m), 741 (m); ^1H NMR ($CDCl_3$) δ 7.10–7.18 (m, 4H), 7.27 (t, J=7.3 Hz, 1H), 7.39 (dd, J=7.3, 0.9 Hz, 1H), 7.52 (t, J=7.0 Hz, 1H), 7.57 (t, J=7.0 Hz, 1H), 7.81 (d, J=7.9 Hz, 1H), 7.84 (unresolved m, 1H), 7.9 (d, J=8.3 Hz, 1H), 7.95 (d, J=8.3 Hz, 1H), 8.3 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 126.7, 127.2, 127.4, 127.8, 127.9, 128.5, 128.8, 129.1, 130.6, 130.8, 131.2 (×2), 133.2, 133.7, 135.0, 149.6; MS (EI) *m/e* (rel intensity) 275 (M^+, 12), 229 (100); HRMS calcd for $C_{18}H_{13}$ ([M−NO_2]$^+$) 229.1017, found 229.1011.

4.2.7. 3-[(*E*)-1-Nitro-2-phenylvinyl)]thiophene (12o). Light yellow solid; yield 0.173 g (75%); mp 102 °C (*n*-hexane); IR (KBr, cm^{-1}) 3103 (w), 2924 (w), 1649 (m), 1511 (s), 1445 (w), 1314 (s), 1212 (m), 768 (m), 752 (m), 688 (s); ^1H NMR ($CDCl_3$) δ 6.98 (dd, J=4.9, 1.3 Hz, 1H), 7.06–7.08 (m, 2H), 7.19 (td, J=5.1, 1.8 Hz, 2H), 7.26 (tt, J=7.7, 1.8 Hz, 1H), 7.33 (dd, J=2.9, 1.3 Hz, 1H), 7.39 (dd, J=4.9, 2.9 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 109.9, 126.8, 128.4, 128.7, 128.8, 129.8, 130.8, 130.9, 131.3, 135.4, 144.7; MS (TOF ES$^+$) *m/e* (rel intensity) 254 (MNa^+, 30), 185 (100); HRMS calcd for $C_{12}H_9NO_2SNa$ (MNa^+) 254.0252, found 254.0237.

4.2.8. (*E*)-2-Nitro-1,3-diphenylbuta-1,3-diene (12p). Dark yellow liquid; yield 0.213 g (85%); IR (film, cm^{-1}) 3055 (s), 2985 (w), 1651 (m), 1523 (s), 1447 (m), 1317 (s), 1265 (s), 1006 (m), 927 (m), 789 (s), 745 (vs), 704 (s); ^1H NMR ($CDCl_3$) δ 5.53 (unresolved, 1H), 6.10 (unresolved, 1H), 7.30–7.42 (m, 5H), 7.47–7.52 (m, 3H), 7.59–7.65 (m, 2H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 121.3, 125.5, 128.8, 128.9, 129.0, 130.9, 131.0, 131.1, 135.7, 136.4, 139.1, 149.2; MS (TOF ES$^+$) *m/e* (rel intensity) 252 (MH^+, 95), 224 (10), 205 (100), 174 (25); HRMS calcd for $C_{16}H_{14}NO_2$ (MH^+) 252.1024, found 252.1025. No coupling is observed between protons resonating at δ 5.53 and 6.10. However, gHSQC confirmed that both protons are attached to the C at δ 121.3.

4.2.9. (*E*)-2-Benzylidene-3-phenylbut-3-enal (14a). Off-white solid; yield 0.191 g (82%); mp 102–103 °C (*n*-hexane–EtOAc–ether 7:1:2); IR (film, cm^{-1}) 3082 (w), 3057 (w), 2924 (w), 2853 (w), 1671 (s), 1630 (m), 1596 (m), 1423 (m), 1148 (m), 791 (m), 713 (m), 685 (m); ^1H NMR ($CDCl_3$) δ 5.15 (s, 1H), 5.88 (s, 1H), 7.15–7.25 (m, 6H), 7.34–7.38 (m, 2H), 7.36 (s, 1H), 7.53 (m, 2H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 116.7, 125.7, 128.2, 128.5, 128.6, 130.5, 130.8, 133.7, 137.3, 141.4, 141.7, 150.2, 193.9; MS (TOF ES$^+$) *m/e* (rel intensity) 235 (MH^+, 100); HRMS calcd for $C_{17}H_{15}O$ 235.1123, found 235.1126.

4.2.10. (*E*)-Ethyl-2-benzylidene-3-phenylbut-3-enoate (14b). Light yellow liquid; yield 0.245 g (88%); IR (film, cm^{-1}) 3058 (w), 3027 (w), 2981 (w), 1711 (vs), 1624 (w), 1494 (w), 1446 (w), 1249 (vs), 1198 (s), 1053 (m), 783 (m), 696 (m); ^1H NMR ($CDCl_3$) δ 1.07 (t, J=7.3 Hz, 3H), 4.08 (q, J=7.3 Hz, 2H), 5.18 (d, J=0.7 Hz, 1H), 5.73 (d, J=0.7 Hz, 1H), 7.15–7.28 (m, 6H), 7.43 (dt, J=6.8, 2.0 Hz, 2H), 7.49–7.53 (m, 2H), 7.8 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 60.9, 116.4, 125.7, 127.8, 128.3, 128.5, 129.2, 130.2, 132.4, 134.4, 138.6, 140.8, 143.3, 167.4; MS (TOF ES$^+$) *m/e* (rel intensity) 279 (MH^+, 35), 249 (100), 233 (38), 205 (2); HRMS calcd for $C_{19}H_{19}O_2$ (MH^+) 279.1385, found 279.1393.

4.3. General procedure for Sonogashira–Hagihara cross-coupling of α-bromonitroalkenes 1 with terminal acetylenes 15 (Table 6)

To a solution of alkyne **15** (0.3 mmol) in toluene (2 ml) was added copper(I) iodide (2.5 mol %), and the reaction mixture was stirred at ambient temperature for 15 min. Meanwhile, a solution of α-bromonitroalkene **1** (0.2 mmol) in toluene (2 ml) was added and the reaction mixture was stirred for 15 min. Now, $Pd(PPh_3)_4$ (24 mg, 2.5 mol %) was added in one portion followed by *N*-methylmorpholine (0.7 ml, 20 equiv, excess) over 1 min. The reaction mixture was slowly warmed to 50–60 °C and the progress of the reaction was monitored by TLC analysis. It was cooled to ambient temperature and diluted with ether and filtered. The organic layer was concentrated in vacuo and the crude product was purified by silica gel column chromatography (EtOAc–hexanes, gradient elution) to provide pure nitroenynes **16**. The solid products of **16** were further purified by recrystallization from ethanol or ether–hexane mixture and stored below 10 °C under N_2.

4.3.1. (*E*)-4-Nitro-5-phenylpent-4-en-2-ynyl benzoate (16a). Light yellow liquid; yield 0.221 g (72%); IR (film, cm^{-1}) 2962 (w), 2927 (w), 2375 (w), 1723 (s), 1528 (m), 1445 (w), 1324 (m), 1265 (s), 1096 (m), 1070 (w), 1026 (w), 711 (m); ^1H NMR ($CDCl_3$) δ 5.28 (s, 2H), 7.40–7.52 (m, 6H), 8.0 (d, J=7.3 Hz, 2H), 8.14 (dd, J=8.2, 1.2 Hz, 2H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.9, 76.2, 97.9, 128.4, 128.5, 129.0, 129.8, 130.1, 131.3, 132.7, 133.4, 133.6, 140.5, 165.6; MS (TOF ES$^+$) *m/e* (rel intensity) 330 (MNa^+, 18); HRMS (TOF ES$^+$) calcd for $C_{18}H_{13}NO_4Na$ (MNa^+) 330.0742, found 330.0753.

4.3.2. (*E*)-2-Nitro-1,4-diphenylbut-1-en-3-yne (16b). Light yellow liquid; yield 0.171 g (69%); IR (film, cm^{-1}) 3054 (m), 2986 (w), 2274 (w), 1633 (w), 1531 (m), 1493 (w), 1422 (w), 1327 (m), 1265 (s), 895 (w), 741 (s), 706 (s); ^1H NMR ($CDCl_3$) δ 7.38–7.58 (m, 6H), 7.60–7.64 (m, 2H), 8.04–8.10 (m, 2H), 8.3 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 79.1, 103.2, 128.6, 129.0, 129.1, 129.3, 129.8, 130.6, 131.1, 131.7, 132.3, 138.3; MS (TOF ES$^+$) *m/e* (rel intensity) 203 ($[M-NO_2]^+$, 3); HRMS (TOF ES$^+$) calcd for $C_{16}H_{11}$ ($[M-NO_2]^+$) 203.0861, found 203.0871.

4.3.3. 1-Fluoro-4-(*E*)-(3-nitro-4-phenylbut-3-en-1-ynyl)-benzene (16c). Light yellow solid; yield 0.200 g (76%); mp 64–65 °C (*n*-hexane); IR (film, cm^{-1}) 3055 (m), 2986 (w), 2250 (w), 1633 (w), 1531 (m), 1492 (w), 1422 (w), 1327 (m), 1265 (s), 895 (w), 741 (s), 706 (s); ^1H NMR ($CDCl_3$) δ 7.13 (t, J=8.5 Hz, 2H), 7.49–7.55 (m, 3H), 7.61 (dd, J=8.2, 5.5 Hz, 2H), 8.03 (dd, J=8.2, 1.8 Hz, 2H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 79.0, 103.4, 116.3, 116.5, 121.1, 127.0 (d, J_{C-F}=3.0 Hz), 128.7, 130.0, 131.8, 133.4 (d, J_{C-F}=8.0 Hz), 136.9, 164.8 (d, J_{C-F}=255.0 Hz); ^{19}F NMR ($CDCl_3$) δ −106.0; MS (TOF ES$^+$) *m/e* (rel intensity) 221 ($[M-NO_2]^+$, 12); HRMS (TOF ES$^+$) calcd for $C_{16}H_{10}F$ ($[M-NO_2]^+$) 221.0767, found 221.0773.

4.3.4. (*E*)-(5-Benzyloxy)-2-nitropent-1-en-3-ynyl)benzene (16e). Light yellow liquid; yield 0.205 g (70%); IR (film, cm^{-1}) 3061 (w), 3032 (w), 2851 (w), 2342 (w), 1626 (m), 1532 (s), 1496 (w), 1451 (m), 1379 (w), 1325 (s), 1266 (w), 1214 (m), 1186 (w), 1118 (m), 1074 (m), 1028 (w), 936 (w), 863 (w), 766 (m), 738 (s), 699 (m), 687 (m); ^1H NMR ($CDCl_3$) δ 4.54 (s, 2H), 4.72 (s, 2H), 7.32–7.41 (m, 5H), 7.43–7.54 (m, 3H), 7.90–8.10 (m, 2H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 57.6, 72.0, 76.3, 100.3, 128.1, 128.2, 128.5, 129.0, 130.3, 131.1, 132.3, 132.5, 136.9, 139.4; MS (TOF ES$^+$) *m/e* (rel intensity) 316 (MNa^+, 100), 230 (28), 229 (21); HRMS (TOF ES$^+$) calcd for $C_{18}H_{15}NO_3Na$ (MNa^+) 316.0950, found 316.0806.

4.3.5. (*E*)-(2-Nitrodec-1-en-3-ynyl)benzene (16f). Light yellow liquid; yield 0.218 g (85%); IR (film, cm^{-1}) 3061 (w), 2930 (s), 2859 (m), 2217 (w), 1610 (w), 1532 (s), 1450 (m), 1380 (w), 1324 (s), 1213 (m), 958 (m), 860 (w), 764 (m), 688 (m); ^1H NMR ($CDCl_3$) δ 0.8 (t, J=6.6 Hz, 3H), 1.20–1.24 (m, 4H), 1.34–1.48 (m, 2H), 1.57 (quintet, J=7.5 Hz, 2H), 2.48 (t, J=7.5 Hz, 2H), 7.31–7.43 (m, 3H), 7.84–7.89 (m, 2H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.9, 22.4, 27.8, 28.5, 31.3, 71.0, 106.2, 128.7, 129.2, 130.7, 131.8, 133.1, 137.0; MS (TOF ES$^+$) *m/e* (rel intensity) 280 (MNa^+, 100), 258 (MH^+, 22), 211 ($[(M-NO_2)^+$, 18); HRMS (TOF ES$^+$) calcd for $C_{16}H_{19}NO_2Na$ $(M+Na)^+$ 280.1313, found 280.1076.

4.3.6. (*E*)-5-(4-Methoxyphenyl)-4-nitropent-4-en-2-ynyl benzoate (16g). Light yellow solid; yield 0.232 g (69%); mp 141 °C (*n*-hexane); IR (film, cm^{-1}) 3054 (w), 2966 (w), 2930 (w), 2344 (w), 1723 (s), 1653 (m), 1637 (m), 1593 (s), 1502 (m), 1427 (w), 1367 (w), 1308 (m), 1267 (s), 1175 (s), 1092 (w), 1067 (w), 1026 (w), 966 (w), 833 (w), 714 (m); ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 5.30 (s, 2H), 6.91 (dt, J=9.3, 2.5 Hz, 2H), 7.48 (td, J=7.3, 1.3 Hz, 2H), 7.61 (tt, J=7.3, 1.3 Hz, 1H), 8.01 (dt, J=9.3, 2.5 Hz, 2H), 8.13 (m, 2H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 53.0, 55.5, 76.7, 97.6, 114.6, 122.7, 128.5, 129.2, 129.7, 129.8, 133.5, 133.8, 140.6, 163.4, 165.8; MS (TOF ES$^+$) *m/e* (rel intensity) 360 (MNa^+, 15), 159 (100); HRMS (TOF ES$^+$) calcd for $C_{19}H_{15}NO_5Na$ (MNa^+) 360.0848, found 360.0845.

4.3.7. (*E*)-5-(Furan-2-yl)-4-nitropent-4-en-2-ynyl benzoate (16h). Light brown solid; yield 0.210 g (70%); mp 77 °C (*n*-hexane–ether 9.5:0.5); IR (film, cm^{-1}) 3063 (w), 2929 (w), 2853 (w), 2343 (w), 1721 (s), 1612 (m), 1523 (m), 1462 (m), 1317 (s), 1265 (s), 1107 (m), 1095 (m), 1070 (w), 769 (m), 709 (m); ^1H NMR ($CDCl_3$) δ 5.30 (s, 2H), 6.62 (dd, J=3.5, 1.4 Hz, 1H), 7.46–7.51 (m, 3H), 7.61 (tt, J=7.5, 1.3 Hz, 1H), 7.67 (d, J=1.4 Hz, 1H), 8.10–8.11 (m, 2H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.9, 76.0, 98.8, 113.9, 120.3, 120.6, 127.8, 128.5, 129.1, 129.8, 133.6, 147.2, 148.0, 165.8; MS (TOF ES$^+$) *m/e* (rel intensity) 320 (MNa^+, 100), 99 (25); HRMS (TOF ES$^+$) calcd for $C_{16}H_{11}NO_5Na$ 320.0535, found 320.0528.

4.3.8. (*E*)-4-Nitro-5-(thiophen-2-yl)pent-4-en-2-ynyl benzoate (16i). Light yellow solid; yield 0.250 g (80%); mp 96–97 °C (*n*-hexane–ether 9:1); IR (film, cm^{-1}) 3045 (w), 2942 (w), 1721 (s), 1603 (s), 1520 (s), 1497 (m), 1452 (w), 1425 (w), 1381 (m), 1331 (m), 1307 (s), 1264 (m), 1248 (m), 1224 (w), 1099 (m), 972 (m), 714 (s), 576 (m); ^1H NMR ($CDCl_3$) δ 5.36 (s, 2H), 7.19 (dd, J=5.0, 3.7 Hz, 1H), 7.48 (t, J=7.5 Hz, 2H), 7.61 (td, J=7.5, 1.4 Hz, 1H), 7.65 (d, J=5.0 Hz, 1H), 7.71 (d, J=3.7 Hz, 1H), 8.11 (dd, J=7.5, 1.4 Hz, 2H), 8.6 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.9, 76.3, 100.8, 128.2, 128.5, 129.1, 129.2, 129.8, 133.5, 134.3, 134.6, 134.7, 137.8, 165.6; MS (TOF ES$^+$) *m/e* (rel intensity) 336 (MNa^+, 100), 279 (2), 192 (2), 134 (3), 108 (5); HRMS (TOF ES$^+$) calcd for $C_{16}H_{11}NO_4NaS$ 336.0306, found 336.0306.

4.3.9. (*E*)-2-(2-Nitrodec-1-en-3-ynyl)thiophene (16j). Dark yellow liquid (crystallizes below 16 °C); yield 0.226 g (86%); IR (film, cm^{-1}) 3061 (w), 2930 (s), 2858 (m), 2217 (m), 1610 (m), 1531 (s), 1450 (m), 1380 (w), 1323 (s), 1213 (m), 957 (m), 860 (w), 764 (m), 688 (s); ^1H NMR ($CDCl_3$) δ 0.9 (t, J=7.0 Hz, 3H), 1.30–1.38 (m, 4H), 1.45–1.54 (m, 2H), 1.73 (quintet, J=7.4 Hz, 2H), 2.65 (t, J=7.4 Hz, 2H), 7.20 (dd, J=5.1, 3.7 Hz, 1H), 7.62 (d, J=3.7 Hz, 1H), 7.67 (d, J=5.1 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.3, 22.5, 27.7, 28.6, 31.2, 71.1, 109.7, 127.9, 130.7, 131.7, 133.2, 135.1, 136.6; MS (MALDI TOF$^+$) *m/e* (rel intensity) 264 (MH^+, 24); HRMS calcd for $C_{14}H_{18}NO_2S$ 264.1058, found 264.1100.

4.3.10. (*E*)-5-(4-Chlorophenyl)-4-nitropent-4-en-2-ynyl benzoate (16l). Light yellow solid; yield 0.260 g (76%); mp 110–111 °C (*n*-hexane); IR (film, cm^{-1}) 3067 (w), 3030 (w), 2925 (m), 2853 (w), 2366 (w), 1688 (s), 1635 (s), 1521 (s), 1453 (m), 1423 (m), 1343 (s), 1093 (m), 1072 (m), 1026 (m), 967 (w), 708 (s); ^{1}H NMR ($CDCl_3$) δ 5.29 (s, 2H), 7.41 (d, J=8.6 Hz, 2H), 7.52 (t, J=7.5 Hz, 2H), 7.65 (t, J=7.5 Hz, 1H), 7.96 (d, J=8.6 Hz, 2H), 8.13 (d, J=7.5 Hz, 2H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.7, 76.0, 98.6, 128.5, 128.6, 129.0, 129.5, 129.9, 132.4, 133.4, 133.7, 138.9, 139.1, 165.8; MS (TOF ES$^+$) *m/e* (rel intensity) 364 (MNa^+, 65), 158 (55); HRMS (TOF ES$^+$) calcd for $C_{18}H_{12}NO_4NaCl$ (MNa^+) 364.0353, found 364.0358.

4.3.11. Diethyl 2-(2-nitro-1,2-diphenylethyl)malonate (22). Method A. To a solution of diisopropyl amine (0.06 ml, 0.53 mmol) in THF (0.5 ml) cooled to 0 °C was added *n*-butyllithium (0.04 ml, 0.56 mmol, 1.5 M in hexanes) over 1 min and the reaction mixture was stirred at 0 °C for 30 min. After cooling to −78 °C, a solution of (±)-BINOL (20 mg, 0.06 mmol) in THF (0.5 ml) was added and the reaction mixture was stirred for 30 min. A solution of diethyl malonate (0.106 g, 0.66 mmol) in THF (1 ml) was added dropwise over 1 min. After stirring the reaction mixture at −78 °C for 1 h, a solution of α-phenylnitrostyrene **12a** (0.075 g, 0.33 mmol) in THF (1 ml) was added dropwise over 5 min and stirring continued at −78 °C for 4 h and at ambient temperature for 8 h. The reaction mixture was quenched with ice-cold aq NH_4Cl (3 ml) and diluted with ether (10 ml). The layers were separated and the aqueous layer was extracted with ether (2×5 ml). The combined organic layers were washed successively with water (5 ml) and brine (5 ml), dried (anhyd Na_2SO_4), and filtered. The organic layer was concentrated in vacuo and the crude residue was purified by silica gel column chromatography using ethyl acetate–hexane (1:10) as eluent to provide chemically pure **22** as a mixture of diastereomers **22a** and **22b** in 5:3.

Method B. A solution of $Mg(OTf)_2$ (32 mg, 0.1 mmol), (±)-BOX ligand[48] (36 mg, 0.1 mmol), and $CHCl_3$ (1 ml) was stirred at rt for 1 h. Then, $CHCl_3$ (3 ml) was introduced followed by powdered molecular sieves (200 mg, 4 Å) and the reaction mixture was stirred for an additional 2 h. Then, α-phenylnitrostyrene **12a** (0.225 mg, 1 mmol), diethyl malonate (1.5 ml, 10 mmol), and NMM (0.02 ml, 0.2 mmol) were introduced in succession. The reaction mixture was then stirred at ambient temperature for 7 days. The reaction mixture was then quenched with saturated aq NH_4Cl (2 ml), diluted with ether (10 ml), and filtered. The organic layer was washed with water (5 ml) and brine (5 ml), dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using EtOAc–*n*-hexane (1:10) as eluent to provide chemically pure **22** as a mixture of diastereomers **22a** and **22b** in 3.2:1.

Major diastereomer **22a** (isolated in pure form by repeated recrystallization of the mixture from ether–hexane 1:7): colorless solid; yield 0.095 g (75%); mp 131–132 °C (ether–hexane 1:7); IR (KBr, cm^{-1}) 3055 (m), 2986 (m), 2931 (w), 1730 (s), 1557 (s), 1497 (w), 1454 (w), 1422 (w), 1368 (m), 1265 (s), 1177 (m), 1031 (w), 737 (s), 703 (s); ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J=7.0 Hz, 3H), 1.05 (t, J=7.0 Hz, 3H), 3.54 (d, J=5.9 Hz, 1H), 3.86 (q, J=7.0 Hz, 2H), 3.88 (q, J=7.0 Hz, 2H), 4.54 (dd, J=11.6, 5.9 Hz, 1H), 6.34 (d, J=11.6 Hz, 1H), 7.27–7.34 (m, 4H), 7.41–7.49 (m, 4H), 7.63–7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.66, 13.71, 48.2, 54.2, 61.56, 61.64, 93.4, 128.3, 128.6, 128.9, 129.99, 129.04, 130.4, 132.0, 135.8, 167.0, 167.3; MS (TOF ES$^+$) *m/e* (rel intensity) 408 (MNa^+, 100), 339 (10), 249 (10), 247 (25); HRMS calcd for $C_{21}H_{23}NO_6Na$ (MNa^+) 408.1423, found 408.1406.

Minor diastereomer **22b** (isolated from the mother liquor via repeated removal of major isomer **22a** by recrystallization from ether–hexane 1:7): colorless viscous oil; yield 0.020 g (15%); IR (film, cm^{-1}) 3056 (s), 2986 (m), 1734 (s), 1557 (s), 1424 (w), 1368 (w), 1265 (s), 1171 (w), 1096 (w), 1027 (w), 896 (m), 742 (s); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J=7.2 Hz, 3H), 1.20 (t, J=7.2 Hz, 3H), 3.90 (d, J=7.0 Hz, 1H), 4.13 (q, J=7.2 Hz, 2H), 4.20 (q, J=7.2 Hz, 2H), 4.62 (dd, J=10.5, 7.0 Hz, 1H), 6.19 (d, J=10.5 Hz, 1H), 7.20–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.9, 48.1, 54.7, 61.7, 62.0, 92.3, 125.3, 127.8, 128.2, 128.5, 128.7, 129.0, 129.6, 129.8, 167.1, 167.5; MS (TOF ES$^+$) *m/e* (rel intensity) 408 (MNa^+, 45), 339 (100), 247 (33); HRMS calcd for $C_{21}H_{23}NO_6Na$ (MNa^+) 408.1423, found 408.1434.

4.3.12. 3,4,5-Triphenylisoxazole 23.[49] To a stirred solution of α-phenylnitrostyrene **12a** (0.038 g, 0.14 mmol), cooled to 0 °C, were added benzaldoxime (0.051 g, 0.42 mmol) in CH_2Cl_2 (5 ml), triethyl amine (0.1 ml, 0.70 mmol), and finally 4% aq NaOCl (5 ml, excess) dropwise over 15 min. The reaction mixture was stirred at ambient temperature for 24 h. The organic layer was separated and washed with 5% aq HCl (10 ml), water (5 ml), and brine (5 ml), dried (anhyd Na_2SO_4), and filtered. The filtrate was concentrated in vacuo and the crude residue was purified by silica gel column chromatography using ethyl acetate–hexane (1:5) as eluent to provide pure **23**. Colorless solid; yield 0.013 g (30%); mp 214–215 °C (lit.[49] mp 215–215.5 °C); IR (KBr, cm^{-1}) 3070 (m), 2925 (w), 1687 (m), 1600 (m), 1450 (s), 1389 (s), 1314 (m), 1291 (m), 1207 (s), 1181 (w), 1026 (m), 931 (m), 770 (s), 691 (s); ^{1}H NMR ($CDCl_3$) δ 7.53–7.70 (m, 9H), 8.49–8.51 (m, 3H), 8.68–8.70 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 120.2, 121.1, 126.6, 127.4, 128.3 (×2), 128.6, 128.9, 129.2, 130.0, 132.7, 133.2, 133.7, 160.9, 170.2; MS (MALDI TOF$^+$) *m/e* (rel intensity) 297 (98); HRMS calcd for $C_{21}H_{15}NO$ (M^+) 297.1154, found 297.2100. Only mp is reported in the literature.[49]

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Supplementary data

It includes experimental procedures for the preparation of terminal acetylenes **15** and bromoalkenes **1** as well as characterization table/data for bromoalkenes **1**. Complete characterization data for the known coupled products **12a–f**. Copies of ^{1}H and ^{13}C NMR spectra for all the new

compounds and some of the known compounds for which experimental data are not available in the literature. Copies of ^{19}F, ^{1}H–^{1}H COSY, and NOESY NMR spectra for selected compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.012.

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